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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Lapidus et al.		
SERIAL NUMBER:	09/545,162	GROUP NUMBER:	1655
FILING DATE	April 7, 2000	EXAMINER:	Juliet C. Einsmann
TITLE:	METHODS FOR DETECTING NUCLEIC ACIDS INDICATIVE OF CANCER		

Commissioner for Patents
Washington, D.C. 20231

AMENDMENT AND RESPONSE

This paper is submitted in response to the Office Action mailed from the U. S. Patent and Trademark Office on November 19, 2001, in which claims were rejected under 35 U.S.C. § 112 first paragraph, 35 U.S.C. § 112 second paragraph and 35 U.S.C. § 102(b). Applicants submit a petition and an appropriate fee for a two month extension of time up to and including April 19, 2002. Reconsideration and withdrawal of the rejections are requested in light of the following amendments and remarks.

In addition, Applicant submits herewith a paper copy of the sequence listing, a computer readable form of the sequence listing and a statement verifying that the content of the paper copy and the computer readable form of the sequence listing are identical.

AMENDMENTS

Prior to further examination of this application, please amend the specification and claims as follows.

In the Specification:

Please amend the specification to introduce a sequence listing. Applicants submit a paper copy of the sequence listing under 37 C.F.R. §§ 1.821-1.825. Applicants respectfully submit that

the introduction of a sequence listing in the specification does not add any new matter. Support for the sequence listing can be found in the specification as filed.

In the Claims:

Please cancel claims 2-5 without prejudice. Please amend claims 7 and 8 and add new claims 10-14.

7. (Twice Amended) A method for screening a patient for cancer or precancer, the method comprising the step of:

detecting in a patient tissue or body fluid sample comprising exfoliated cells a fragment of a nucleic acid that is present in both normal and cancerous or precancerous cells, wherein said fragment is of a length that is greater than a length of said nucleic acid expected to be present in a sample from a healthy patient;

the presence of the fragment being a positive screen for cancer or precancer.

8. (Amended) A method for screening a patient for cancer or precancer, the method comprising the steps of:

determining in a patient tissue or body fluid sample comprising exfoliated cells or cellular debris whether an amount of a DNA fragment greater than 200 base pairs in length exceeds a predetermined amount, wherein said DNA fragment is a degradation product of DNA that is present in both normal and cancerous or precancerous cells; and,

identifying a positive screen for cancer or precancer if said amount does exceed the predetermined amount.

10. (New) The method of claim 7, wherein said detecting step comprises conducting an amplification reaction designed to amplify only nucleic acid fragments that are greater than 200 base pairs in length.

11. (New) The method of claim 7, wherein said sample is selected from the group consisting of stool, pus, and urine.

12. (New) The method of claim 7, further comprising the step of enriching said sample for human DNA.

13. (New) The method of claim 7, further comprising the step of isolating human DNA from said sample.

14. (New) The method of claim 9, wherein said sample comprises stool.

REMARKS

Rejections of the Claims

Claims 2-5 and 7-9 were considered. Claims 2-5 were rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claim 9 was rejected under 35 U.S.C. § 112, first paragraph, for not enabling a person skilled in the art to which it pertains to use the invention commensurate in scope with the claim. Claim 7 was rejected under 35 U.S.C. 102 (b) as being anticipated by U.S. Patent No. 5,645,995 to Kieback et al. (hereafter "Kieback"). Claim 8 was rejected under 35 U.S.C. 102 (b) as being anticipated by Ditkoff, et al. (Surgery 120: 959-965, 1996) (hereafter, "Ditkoff"). Claim 8 was also rejected 35 U.S.C. 102 (b) as being anticipated by Smith-Ravin et al. (Gut 1995; 36: 81-86) (hereafter, "Smith-Ravin"). Claims 7-9 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 in U.S. Patent No. 6,143,529.

Upon entry of the present amendments, claims 7-14 are pending in this application. The claims are amended to further clarify the claimed subject matter. Claims 2-5 are canceled without prejudice and without any intention to abandon the subject matter as filed, but with the intention that claims of the same, greater, or lesser scope may be pursued in this or a continuing application. Support for the amendments to claims 7 and 8 can be found in the specification and claims as originally filed, *inter alia*, at page page 3, lines 2-26, page 11, lines 27-19 to page 12, lines 1-7 and page 12, lines 3-7 and lines 12-14, and page 15, lines 1-7. Support for new claims

10-14 can be found in the originally filed specification, *inter alia*, at page 14, lines 20-21; page 18, lines 18-20; page 6, lines 13-14; page 13, lines 22-23 and originally filed claims 4 and 5.

I. Claim Rejections Under 35 U.S.C. § 112 Second Paragraph

Claims 2-5 were rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants hereby cancel claims 2-5 without prejudice. Therefore, Applicants respectfully request that this rejection of claims 2-5 under 35 U.S.C. § 112 be reconsidered and withdrawn.

II. Claim Rejections Under 35 U.S.C. § 112 First Paragraph

Claim 9 was rejected under 35 U.S.C. § 112, first paragraph for failing to enable a person skilled in the art to use the invention commensurate in scope with the claim. According to the Office Action, neither the specification nor the prior art provide any evidence of a universal association between a ratio of nucleic acids greater than 200 base pairs to nucleic acids shorter than 200 base pairs and every cancer and every body fluid, and would therefore require extensive experimentation on part of a practitioner wishing to demonstrate such an association.

The proper standard of enablement under 35 U.S.C. § 112, first paragraph, is whether one skilled in the art could make and use the invention without undue experimentation based on the disclosure in the patent application coupled with information known in the art. This standard does not require an applicant to describe in an application every conceivable embodiment of the invention. Rather the enablement requirement is met when there is a reasonable belief that applicant's success with one embodiment of the invention could be extrapolated to other embodiments by one skilled in the art at the time of the invention.

Applicants respectfully submit that the methods of the claimed invention can be extrapolated to any tissue or body fluid that comprises exfoliated cells or cellular debris, as

recited in claim 9. The specification contains teachings of the use of the methods of the claimed invention on any tissue or body fluid containing exfoliated cells or cellular debris. Support for such a tissue or body fluid comprising exfoliated cells other than stool and a cancer or precancer other than colorectal cancer can be found in the specification as filed, *inter alia*, at least at page 5, second full paragraph and page 11, second and third full paragraphs.

II. Claim Rejections Under 35 U.S.C. § 102

A. Rejection of claim 7 as anticipated by Kieback

Claim 7 was rejected under 35 USC § 102(b) as anticipated by Kieback. Claim 7 has been amended to clarify that a positive screen for cancer or precancer is identified when a fragment of a nucleic acid that is present in both normal and cancerous and precancerous cells is detected in a patient sample comprising exfoliated cells, provided that the fragment is of a length greater than the length of the nucleic acid expected to be found in a healthy patient. Accordingly, Applicants traverse this rejection to the extent that it is maintained over the claims as amended.

Applicants respectfully submit that Kieback discloses a method that involves detecting the presence of mutant DNA having an insertion (human progesterone receptor gene containing an Alu insertion), thus making its length greater than the length of normal or non-mutant DNA expected in a healthy patient. Accordingly, Applicants respectfully submit that Kieback does not teach or suggest, expressly or impliedly, the detection of a fragment of a nucleic acid that is *present in both normal as well as cancerous or precancerous cells,* as the basis of a screen for cancer or precancer in a patient. In contrast, Kieback teaches methods for diagnosing a sample as being positive for disease based on the detection of a mutant DNA in a disease sample. Applicants respectfully submit that the mutant DNA of Kieback is not a fragment of a nucleic acid that is *present in both normal as well as cancerous or precancerous cells.*

Therefore, Kieback fails to disclose every element of the amended claim 7 and cannot form the basis for continued rejection under 35 U.S.C. § 102(b). Based on the above arguments, Applicants respectfully request that this rejection be reconsidered and withdrawn.

B. Rejection of claim 8 as anticipated by Ditkoff

Claim 8 was rejected under 35 USC § 102(b) as anticipated by Ditkoff. Claim 8 has been amended to clarify that a positive screen for cancer or precancer is identified when an amount of DNA fragment greater than 200 base pairs in length exceeds a predetermined amount, where the DNA fragment is a degradation product of DNA that is present in both normal and cancerous or precancerous cells. Accordingly, Applicants traverse this rejection to the extent that it is maintained over the claims as amended.

Applicants respectfully submit that Ditkoff discloses a method that involves detecting the presence of an *mRNA* (the thyroglobulin transcript) in order to detect the presence of circulating malignant thyroid cells in a blood sample. However, Ditkoff fails to teach or suggest a method for detecting cancer or precancer based solely on the amount of a *DNA* fragment greater than a certain length in a patient tissue or body fluid sample containing exfoliated cells or cellular debris. The Office Action points to the 529 bp fragment disclosed in Fig. 2A of Ditkoff. However, Applicants respectfully submit that the method in Ditkoff is based on detecting the presence of the thyroglobulin *mRNA* versus an absence of the thyroglobulin *mRNA* as indicated in the legend of Fig. 2A. Accordingly, Ditkoff fails to specifically teach or suggest a method to screen a patient for cancer or precancer based on detecting the amount of a *DNA* fragment greater than 200 base pairs in length, wherein the DNA fragment is a degradation product of DNA that is present in both normal and cancerous or precancerous cells.

Accordingly, Applicants respectfully submit that Ditkoff fails to disclose every element of the amended claims and cannot form the basis for continued rejection under 35 U.S.C. § 102(b). Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

C. Rejection of claim 8 as anticipated by Smith-Ravin

Claim 8 was rejected under 35 USC § 102(b) as anticipated by Smith-Ravin. As discussed above, claim 8 has been amended to clarify that that a positive screen for cancer or precancer is identified when an amount of a DNA fragment greater than 200 base pairs in length exceeds a predetermined amount, wherein the DNA fragment is a degradation product of DNA that

is present in both normal and cancerous or precancerous cells. Accordingly, Applicants traverse this rejection to the extent that it is maintained over the claims as amended.

Applicants respectfully submit that Smith-Ravin discloses detecting the presence of specific point mutations (mutations at the first and second based of codon 12 of the *ras* gene) as disclosed in the second column on page 83 of Smith-Ravin. In addition, these point mutations are detected by amplifying fragments 161 bp and 146 bp, respectively. Accordingly, Smith-Ravin fails to teach or suggest a method for detecting cancer or precancer based on a determination of an amount of a DNA fragment longer than 200 base pairs in a patient tissue or body fluid sample containing exfoliated cells or cellular debris, where the DNA fragment is a degradation product of DNA that is found in both normal and cancerous or precancerous cells. Furthermore, Smith-Ravin fails to teach or suggest, expressly or impliedly, a method for detecting cancer or precancer based solely on the length, as opposed to the identity, of a nucleic acid present in such a sample. Therefore, Applicants respectfully submit that Smith-Ravin fails to specifically teach or suggest a method based on detecting an amount of a DNA fragment that is greater than a predetermined amount, wherein the DNA fragment is a degradation product of DNA that is present in both normal and cancerous or precancerous cells.

Accordingly, Applicants respectfully submit that Smith-Ravin fails to disclose every element of the amended claims and cannot form the basis for continued rejection under 35 U.S.C. § 102. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

III. Non-statutory double patenting rejection

Claims 7-9 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 of U.S. Patent No. 6,143,529.

Applicants respectfully request that this rejection be held in abeyance until a determination of allowable subject matter is made.

CONCLUSION

Applicants submit that claims 7-14 are in condition for allowance and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record. Applicants believe that no additional fees are due with this Amendment and Response. However, Applicants hereby authorize the Director to charge any deficiency in the required fees to Deposit Account No. 20-0531.

Respectfully submitted,

Dated: April 19, 2002

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